Most rapid cognitive decline in ApoE ε4 negative Alzheimer’s disease with early onset

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Abstract

Background
We aimed to compare the rate of cognitive decline in patients with early- and late-onset Alzheimer’s disease (AD) and to investigate the potentially modifying influence of ApoE genotype.

Methods
We included 99 patients with early-onset AD (age ≤ 65 years) and 192 patients with late-onset AD (age > 65 years) who had at least 2 MMSE scores (range 2-14) obtained at least one year apart. Linear mixed models were performed to investigate the rate of cognitive decline dependent on age-at-onset and ApoE genotype.

Results
Mean (SD) age for patients with early onset was 57.7 (4.5) years, and 74.5 (5.1) for patients with late onset. Age-at-onset was not associated with baseline MMSE ($\beta$(SE) = 0.8 (0.5), $p = 0.14$). However, patients with early onset showed faster decline on the MMSE of ($\beta$(SE)) 2.4 (0.1) points/year, whereas those with late onset showed decline of 1.7 (0.1) points/year ($p = .00$). After stratification according to ApoE genotype, ApoE ε4 non-carriers with early onset showed faster cognitive decline than non-carriers with late onset (2.4 (0.3) versus 1.3 (0.3) points/year, $p = .01$). In ApoE ε4 carriers, no difference in rate of cognitive decline was found between patients with early and late onset ($\beta$(SE) = 0.2 (0.2), $p = 0.47$).

Conclusion
Patients with early-onset AD show more rapid cognitive decline than patients with late-onset, suggesting that early-onset AD follows a more aggressive course. Furthermore, this effect seems to be most prominent in patients with early onset that do not carry the genetic ApoE ε4 risk factor for AD.
Introduction
Alzheimer’s disease (AD) is the most common form of dementia, characterized by gradually increasing cognitive impairment. Typically, AD is regarded as a disease occurring at old age and estimates of prevalence and incidence do indeed increase exponentially with advancing age. However, AD also affects younger people (under the age of 65 years), commonly referred to as early-onset AD. Although it has been suggested that early onset AD follows a more aggressive course than late-onset AD, only few studies have actually addressed this possible difference and results are conflicting, with one study showing a faster cognitive decline in young, and the other in older patients.

The apolipoprotein E gene (ApoE) is an important risk factor for AD. Presence of the ε4 allele increases the risk of AD and has been associated with an earlier age-at-onset, although this association may be less pronounced in patients under the age of 65 years. Conflicting results have been found with regard to the relation between ApoE ε4 and rate of cognitive decline in AD patients, with studies reporting slower, faster and the same rate of cognitive decline in ApoE ε4 carriers compared to non-carriers.

The aim of this study was to compare the rate of general cognitive decline as measured by the Mini-Mental State Examination (MMSE) between AD patients with early disease onset and those with late disease onset. Furthermore, we investigated the additional influence of ApoE genotype on the rate of cognitive decline.

Methods
Subjects
We studied consecutive patients with sporadic AD from the outpatient memory clinic of the Alzheimer Center of the VU University Medical Center (VUmc). At baseline, all patients had undergone a standardized dementia assessment including medical history, informant-based history, physical and neurological examination, laboratory tests, neuropsychological testing, electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain. Diagnoses of probable AD were made in a multidisciplinary consensus meeting according to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRSA) diagnostic criteria. Patients aged 65 years or less at diagnosis were considered to have early-onset AD and patients above 65 years old were considered to have late-onset AD. The duration of the cognitive complaints as reported by the patient and/or caregiver were recorded to estimate the disease duration at the time of diagnosis. To be included in this study patients had to have at least 2 MMSE scores obtained no less than one year apart. The resulting data set included 1194 MMSE scores from 291 patients. Follow-up time varied between one and six years (mean = 2.3; SD = 1.1) and patients had a median of 3 visits (range: 2-14).
The study was approved by the local Medical Ethical Committee. All patients gave written informed consent for their clinical data to be used for research purposes.

ApoE

ApoE genotype was determined according to the following procedure. DNA was isolated from 10 ml EDTA blood. ApoE genotype was determined at the Department of Clinical Chemistry of the VUmc with the Light Cycler ApoE mutation detection method (Roche Diagnostics GmbH, Mannheim, Germany). ApoE data were available for 185 patients (early onset: n = 69; late onset: n = 116) and were analysed according to the presence or absence of an ApoE ε4 allele.

Statistical analysis

Statistical analyses were performed using SPSS 15.0. For group comparisons at baseline, χ²-tests, Mann-Whitney tests and t-tests were used when appropriate. Linear mixed models were used to assess associations between age-at-onset (≤ 65 years or > 65 years) and the rate of cognitive decline as measured by MMSE. This approach has increased statistical power as it accounts for within-person correlations over time, allows different numbers of assessments, and accounts for varying time intervals between assessments. All assessments, including baseline, were taken into account. A random intercept was assumed, i.e. baseline MMSE was allowed to vary between patients. The first model included terms for age-at-onset, time, sex, and the interaction between age-at-onset and time, with MMSE score as dependent variable. From this model, baseline MMSE and annual change in MMSE for young and old patients could be estimated. The analysis was repeated after stratification according to ApoE ε4 status, so that the effect of age-at-onset on decline in MMSE over time could be estimated separately for ApoE ε4 carriers and non-carriers.

Results

Ninety-nine (34%) patients had early-onset AD and 192 (66%) had late-onset AD (table 1). Mean age for the patients with early onset was 57.7 years, for the patients with late onset it was 74.5 years. Groups did not differ according to sex. Patients with early-onset AD had longer disease duration than patients with late-onset AD (t = 2.1, p = .04). No differences in baseline MMSE were found according to age-at-onset (t = -1.7, p = .10).
We used linear mixed models to compare annual change in MMSE dependent on age-at-onset (≤ 65 years or > 65 years). Age-at-onset was not associated with baseline MMSE ($\beta$(SE) = 0.8 (0.5), $p = .14$). However, an interaction between age-at-onset and time ($\beta$(SE) = 0.6 (0.2), $p = .00$) was found. AD patients with early onset were prone to a faster disease progression (estimated decline in MMSE = -2.4 (SE = 0.1) points per year) than late-onset AD patients (-1.7 (SE = 0.1) points per year).

Subsequently, patients were stratified according to ApoE genotype, to assess the effect of age-at-onset on MMSE score over time for ApoE ε4 carriers and non-carriers separately (Figure 1). Of the non-carriers, 22 (43%) had early disease onset and 29 (57%) had late onset. Linear mixed models showed no association of age-at-onset with baseline MMSE ($\beta$(SE) = 0.9 (1.2), $p = 0.45$), but an interaction between age-at-onset and time ($\beta$(SE) = 1.1 (0.4), $p = .01$) was found. AD patients with early onset were prone to a faster disease progression (estimated decline in MMSE = 2.4 (SE = 0.3) points per year) than late-onset AD patients (1.3 (SE = 0.3) points per year).

Of the ApoE ε4 carriers, 47 (35%) patients had early disease onset and 87 (65%) had late onset. Age-at-onset was associated with baseline MMSE ($\beta$(SE) = 1.7 (0.8), $p = 0.05$). Patients with early onset had lower baseline MMSE ($\beta$(SE) = 21.3 (1.3)) than patients with late onset ($\beta$(SE) = 23.0 (1.3)). There was no interaction between age-at-onset and time, implying similar decline over time ($\beta$(SE) = 0.2 (0.2), $p = 0.47$).

### Table 1. Baseline demographic and clinical characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Early-onset AD</th>
<th>Late-onset AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>99</td>
<td>192</td>
</tr>
<tr>
<td>Sex, n (%) female</td>
<td>50 (51%)</td>
<td>96 (50%)</td>
</tr>
<tr>
<td>Age at diagnosis, mean (SD)</td>
<td>57.7 (4.5)</td>
<td>74.5 (5.1)**</td>
</tr>
<tr>
<td>Duration (years), mean (SD)</td>
<td>3.2 (2.0)</td>
<td>2.7 (2.2)*</td>
</tr>
<tr>
<td>ApoE ε4 positives, n (%)</td>
<td>47 (68%)</td>
<td>87 (75%)</td>
</tr>
<tr>
<td>MMSE at baseline, mean (SD)</td>
<td>21.1 (4.5)</td>
<td>22.0 (4.0)</td>
</tr>
<tr>
<td>Follow-up time (years), mean (SD)</td>
<td>2.5 (1.2)</td>
<td>2.3 (1.0)*</td>
</tr>
<tr>
<td>Number of visits, median (range)</td>
<td>4 (2-10)</td>
<td>3 (2-14)</td>
</tr>
</tbody>
</table>

MMSE = Mini Mental State Examination

* ApoE data available for 185 patients

* $p < .05$, ** $p <.01$
Estimated regression lines of MMSE-score by time for early onset AD and late onset AD, stratified according to ApoE genotype. In ApoE ε4 carriers, early- and late-onset patients show similar rates of cognitive decline. By contrast, in non-carriers, early-onset patients show faster rate of cognitive decline than late-onset patients.

Discussion
We found that AD patients with early disease onset showed faster cognitive decline than patients with late onset, while patients with early- and late-onset AD did not differ according to disease severity at the time of diagnosis. This provides support for the hypothesis that early-onset AD runs a more aggressive course than late-onset AD. Moreover, we found that the effect of age-at-onset was mostly attributable to ApoE ε4 non-carriers. ApoE ε4 non-carriers with early onset showed faster cognitive decline than non-carriers with late-onset AD. This effect was not found in ApoE ε4 carriers; patients with early and late onset showed similar rates of cognitive decline.

Based on clinical observations, it has been suggested that young AD patients show faster cognitive decline than older AD patients. However, actual studies on the difference in cognitive decline between AD patients with early onset and those with late onset are scarce and their conclusions are conflicting. Our findings are consistent with a previous study in a relatively small sample, in which young AD patients showed faster decline on an extended version of the MMSE (max. score = 57) than older AD patients. By contrast, another study reports a faster rate of cognitive decline in late onset AD patients. However, the number of patients with follow-up data in this study was relatively small and the distribution of patients
according to age-at-onset was unclear. Furthermore, the authors state that although rate of progression was more rapid in late-onset AD, considerable overlap among values for the two patient groups was observed, which led them to conclude that age-at-onset is not a strong predictor of rate of progression of dementia in patients with AD. The present study contains a large sample of AD patients with considerable follow-up, and a clear effect of age-at-onset on the rate of cognitive decline was shown.

Furthermore, we showed that the effect of age-at-onset on the rate of cognitive decline is attributable to ApoE ε4 non-carriers, and not so much to ApoE ε4 carriers. In non-carriers, early-onset patients show a doubled rate of cognitive decline compared to late-onset patients, while younger and older ApoE ε4 carriers have a similar rate of decline. The conflicting results with regard to the relation between ApoE genotype and rate of cognitive decline in AD patients which have been reported by previous studies may well be explained by this effect. Since these previous studies either included only late-onset AD patients \(^{15,18}\), or made no distinction between patients with early and late onset \(^{16,17,19}\), they may have missed the rather sensitive modifying effect of ApoE genotype.

Our finding of early-onset ApoE ε4 non-carriers showing the fastest cognitive decline is in line with a previous study by our group which reported that younger age, absence of ApoE ε4, and low MMSE at baseline were associated with higher whole-brain atrophy rate \(^{21}\). It is feasible that patient with early onset and absence of ApoE ε4 do not only show a faster cognitive decline, but also have a higher rate of whole-brain atrophy. Although the presence of ApoE ε4 is a risk factor for developing AD, our data suggest that, especially in patients with early onset, this same presence protects patients, once they actually have the disease.

It is possible that the patients with early-onset AD presented at our memory clinic when they had progressed further into the disease process than the late-onset AD patients. This would explain their faster cognitive decline, since baseline disease severity has been shown to predict the rate of subsequent cognitive decline \(^{22,23}\). However, we do not think this explains our findings, as the disease severity as measured by the MMSE at baseline was similar for patients with early-onset AD and late-onset AD.

The question whether early and late AD should be considered as two subtypes of the same disorder or as two separate disorders is still under debate \(^{24}\). It should be noted that the age of 65 years used in this and most other studies to distinguish early disease onset from late onset is arbitrary. It has been shown that early and late onset AD patients share the presence of amyloid plaques, neurofibrillary tangles and neuronal loss, which indicates the same underlying neuropathology \(^{25}\). However, the difference we found in rate of cognitive decline between both groups, especially in ApoE ε4 non-carriers, might be considered as an argument to regard early and late onset AD as two entities, with specific characteristics.
It might be speculated that in some AD patients, the disease process is so aggressive that it becomes apparent early in life, resulting in early onset of the disease. The faster rate of cognitive decline in young patients might then be explained by this more aggressive process.

Among the limitations to this study is the fact that no post mortem data were available. Therefore, it cannot be excluded that some patients were misdiagnosed as having AD, which might have contaminated the data. At baseline, however, all patients were clinically characterized in a uniform manner, and all patients fulfilled clinical criteria for AD. Another limitation is the fact that age-at-onset is clearly confounded by the patient’s biological age. In this data set, it is not possible to tackle the associations between the two. However, considering biological age in relation to change in cognition, one would expect older patients to show more cognitive impairment, since it is well known that even healthy persons of old age show more cognitive decline than younger healthy persons. In this study, the opposite effect was found in AD patients: the patients with early onset showed more cognitive decline than the patients with late onset. Strengths of the current study include the relatively large group of AD patients that was followed for an average duration of over two years. Furthermore, the applied statistical method of linear mixed models allowed use of all available MMSE’s, up to 14 per patient.

In conclusion, we found that patients with early-onset AD deteriorate faster than AD patients with late onset. The effect of age-at-onset differs between ApoE ε4 carriers and non-carriers. In ApoE ε4 carriers, patients with early and late onset show similar rates of decline. However, ApoE ε4 non-carriers with early onset show a far steeper cognitive decline than non-carriers with late onset. This adds to the notion that AD is to be considered as a heterogeneous disorder with regard to clinical features and disease course. An aggressive disease course is most prominent in patients with early-onset AD that do not carry the genetic risk factor for AD.

Reference list


